DETAILED ACTION

Claims 1-8 are presented for examination.

Objection to the Oath/Declaration

The oath or declaration filed August 5, 2005 is defective because the declaration contains handwritten changes that have not been initialed or dated by the individual(s) who executed the declaration. A new oath or declaration in compliance with 37 C.F.R. 1.67(a) identifying this application by serial number and filing date is required. Please reference MPEP §§602.01 and 602.02.

Objection to the Claims

Claim 3 is objected to for reciting the phrase "...which comprises administering to a said human in need of such treatment...", which is grammatically awkward. Applicant may wish to consider amending the claim to read ---which comprises administering to ~~a~~ said human in need of such treatment--- to clarify the claim language, but is notified that the adoption of such a suggestion does not necessarily obviate any other objection and/or rejection set forth herein the instant Office Action.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-2 and 7-8 are rejected under 35 U.S.C. 101 because the claim recites a method (i.e., a "process" as provided for in 35 U.S.C. 101) without setting forth any steps involved in said process and, thus, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See, for example, *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F.Supp. 131, 149 USPQ 475 (D.D.C. 1996).

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of anaplastic thyroid carcinoma using the instantly claimed compound 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for curing the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

For the purposes of consideration under 35 U.S.C. 112, first paragraph, it is noted that the instant specification defines the term "treatment" as used in the claims as also circumscribing the aspect of curing

the claimed disease. Please see p.2, penultimate paragraph, of the instant specification, which states, "The term 'treatment' comprises the administration of SALT I to a warm-blooded animal in need of such treatment with the aim to cure the tumor or to have an effect on tumor regression or on the delay of progression of a disease." Accordingly, in view of such a definition provided by Applicant, the claims are understood to also include curing anaplastic thyroid carcinoma.

The presently claimed invention is directed to a method for treating human suffering from anaplastic thyroid carcinoma comprising administering to said human in need of such treatment a dose, effective against said disease, of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt thereof.

In particular, one skilled in the art could not practice the presently claimed subject matter of curing anaplastic thyroid carcinoma by administering the claimed compound 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt thereof without undue experimentation because the artisan would not accept on its face that curing anaplastic thyroid carcinoma could actually be achieved given the state of the art at the time of the invention. Based upon the state of the art, as discussed below, and the evidence presented by Applicant, the artisan would have only accepted that the condition could, at best, be treated with the compound as instantly claimed.

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112, *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support;* assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection

can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

The present claims circumscribe the use of the presently claimed compound for curing anaplastic thyroid carcinoma. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed compound that anaplastic thyroid carcinoma would actually be cured or eliminated completely. Because such curative success is not reasonably possible with most diseases or disorders, especially a condition as complex, poorly understood and difficult to treat as anaplastic thyroid carcinoma, the specification, which lacks any direction or guidance as to how the embodiment of curing anaplastic thyroid carcinoma could actually be achieved, is viewed as lacking an enabling disclosure of the entire scope of the claimed invention.

Regarding curing anaplastic thyroid carcinoma, the objective truth that anaplastic thyroid carcinoma can be cured is doubted because the complexity of the disorder and the general lack of response to conventional chemotherapeutic regimens poses a significant challenge to achieving the treatment, let alone the cure, of the disease. While it may be true that there are therapies with extremely limited efficacy to treat such a condition, the art most definitely fails to recognize any therapeutic modality that is capable of curing anaplastic thyroid carcinoma.

In this regard, Stassi et al. ("Thyroid Cancer Resistance to Chemotherapeutic Drugs via Autocrine Production of Interleukin-4 and Interleukin-10", *Cancer Research*, 63; October 15, 2003:6784-6790) is cited. Stassi et al. teaches that, "Thyroid cancer is the most common endocrine malignancy and is responsible for about 60% of deaths secondary to endocrine cancer (1,2). Three major types of malignant tumors originate from the thyroid epithelium. The more differentiated PTCs and FTCs account for most of the malignant tumors, whereas the UTCs are extremely rare (3). Clinical trials with chemotherapeutic drugs have produced only rare and limited positive responses in thyroid cancer (4-6). The expression of the multidrug resistance gene is altered in a small subset of thyroid carcinomas (7-9), but the molecular

bases implicated in the failure of chemotherapy-based regimens have not been defined in the vast majority of thyroid carcinomas." (col.1, para.2, p.6784) Stassi et al. further teaches that, "The poor cytotoxic effect of chemotherapy on thyroid cancer has directed most of the nonsurgical therapeutic efforts on radioiodine therapy, which exploits the iodide uptake potential of thyroid follicular cells to deliver iodine-131 to well-differentiated thyroid cancer cells (2,41). However, a significant number of patients do not respond to radioiodine and have a very poor prognosis (42). The sensitization of thyroid cancer cells to chemotherapy may dramatically improve the survival rate of these patients, whereas targeting the ability of thyroid cancer cells to exploit IL-4 and IL-10 as survival factors may provide a powerful support to alternative treatments." (col.1, para.4, p.6789)

Given that the art expressly acknowledges that the effective treatment, let alone the cure, of anaplastic thyroid carcinoma has not yet been an outcome possible to achieve, the skilled artisan would have recognized that the state of the art with regard to such an objective is not well defined, and is, therefore, unpredictable, such that one of ordinary skill in the art would not accept on its face Applicant's statement that anaplastic thyroid carcinoma could be cured because the pathophysiology of such a condition is particularly complicated, rarely responds to chemotherapeutic and nonchemotherapeutic treatment regimens and, as of the time of the invention, such an objective had been impossible to achieve. In light of such, the artisan would have required sufficient direction as to how the administration of the presently claimed compound could actually cure the disease without requiring an undue level of experimentation such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected given that the cure of the disease is not an outcome reasonably expected by one of ordinary skill in the art and, further, Applicant has failed to provide any guidance to this effect. Absent this disclosure, the present specification fails to enable the full scope of this invention as it related to the objective of curing the disease and, thus, fails to rebut the presumption of unpredictability in the art with regard to this same objective.

It is in this regard that Applicant is directed to the MPEP at §2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involved the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

Applicant provides various examples testing the activity of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide mesylate in suppressing and inducing S-G2 transition cell arrest in anaplastic thyroid cells, inhibiting the tyrosine kinase activity of c-Abl, PDGR receptor and c-kit, effects on cell cycle regulatory proteins in several thyroid cancer cell lines, and the *in vivo* effect in FRO cells implanted into athymic mice, as well as presenting data directed to a clinical Phase I/II study of the compound in the treatment of patients with refractory progressive thyroid carcinoma (see, e.g., Example 4). Please see, e.g., p.4-16 of the instant specification. However, none of these studies demonstrates the ability of the claimed compound to effectively cure anaplastic thyroid carcinoma *per se*. While a lack of a working embodiment cannot be the sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the presently claimed subject matter, in light of the unpredictable nature of the art and the direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole. The instant specification conspicuously lacks any disclosure or teaching of manner and process of using the presently claimed compound for achieving the objective of curing anaplastic thyroid carcinoma itself. Nowhere does the specification disclose the manner or procedure of using the presently claimed compound 4-(4-methylpiperazin-1-ylmethyl)-N-[4-

methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide for curing anaplastic thyroid carcinoma such that the skilled artisan would have been imbued with at least a reasonable expectation of success in achieving such objective(s) without the burden of an undue level of experimentation.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the pharmaceutical and chemical arts that experimentation in this particular art is not at all uncommon, but that the level of experimentation required in order to practice this aspect of the invention in the absence of any enabling direction by Applicant would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added)

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the objective of curing anaplastic thyroid carcinoma in a subject using the claimed compound4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt thereof, could be achieved. In order to actually achieve such a result, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the presently claimed invention.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claims 1-2 and 7-8 provide for a method for the manufacture of a medicament for the treatment of anaplastic thyroid carcinoma, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process Applicant is intending to encompass. A claim is indefinite where it merely recites a purpose or objective without reciting any active, positive steps delimiting how this purpose or objective is actually accomplished.

Because claims 1-2 and 7-8 fail to set forth any steps, the claims will not be further treated with prior art since the method which Applicant is intending to claim has not been clearly described.

Claims 3-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 3 is directed to a method of treating humans suffering from anaplastic thyroid carcinoma, comprising administering to said human in need of such treatment a dose, effective against said disease, of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt thereof.

In particular, the claims fail to precisely or clearly define in whom the method is practiced. For example, the preamble objective of the claims recites the treatment of "humans" (i.e., more than one human, due to the use of the plural term "humans") suffering from anaplastic thyroid carcinoma, but the active step of the claim recites the administration to "said human in need of such treatment" (i.e., a single human, due to the use of the singular term "human"). As a result, it is unclear whether the method of the instant claims is intended to encompass the treatment of a single human subject in need of treatment of anaplastic thyroid carcinoma or whether it is intended to encompass the treatment of multiple human

subjects in need of treatment of anaplastic thyroid carcinoma. Due to such ambiguity in the claims, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection. Clarification is requested.

For the purposes of examination and the application of prior art, claims 3-6 will be interpreted to read upon the treatment of *a* human subject in need of treatment of anaplastic thyroid carcinoma.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 4 is directed to the method according to claim 3, wherein a daily dose of 50 to 600 mg of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of formula I is administered to an adult.

In particular, it is unclear if the "an adult" to whom the compound 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide is being administered is the human subject in need of treatment of anaplastic thyroid carcinoma as required by claim 3, but further limited to an adult. The antecedent basis for the term "an adult" as provided for in instant claim 4 is not clearly defined because the claim fails to indicate whether this same adult subject to whom the compound is being administered is, in fact, also a human subject in need of treatment of anaplastic thyroid carcinoma. Clarification is requested.

For the purposes of examination and the application of prior art, the term "an adult" will be interpreted to be the same human subject treated in instant claim 3.

Claims 4-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, it is unclear if the phrase "of formula I" as recited in each of claims 4-7 is intended to further limit or alter the chemical compound 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide recited in the claim because the claim(s) fail to set forth what, in fact, "formula I" is intended to encompass. In other words, the claims fail to clearly set forth whether the phrase "of formula I" is simply intended to convey the structure of said benzamide compound or if it is intended to convey a structural difference or alteration of said benzamide compound (which, incidentally, if this were the case, would not be adequately conveyed since the claim is silent as to the identity of "formula I"). As a result, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection.

For the purposes of examination and the application of prior art (only with regard to claims 3-6), the claims will be interpreted to read upon the compound 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide *per se*.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

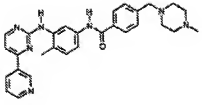
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner

to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman et al. (WO 99/03854; 1999) in view of Ramsden JD ("Angiogenesis in the Thyroid Gland", *Journal of Endocrinology*, 166; 2000:475-480).

Zimmerman et al. teaches the beta-crystal form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyrid-3-yl)pyrimidin-2-ylamino)phenyl]benzamide



methanesulfonate of the formula , an inhibitor of cellular processes involving tyrosine kinases, such as, e.g., c-kit receptor kinase (p.17, para.1), and pharmaceutical preparations thereof containing an effective amount of the compound in combination with a pharmaceutically acceptable carrier (p.17-18, bridging paragraph). Zimmerman et al. further teaches methods for the inhibition of tyrosine kinases, such as, e.g., c-kit receptor kinase, and/or the treatment of warm-blood animals suffering from tumor diseases, wherein a quantity of the beta-crystal form of the methanesulfonic acid addition salt of the compound of the formula set forth *supra* effective against the disease concerned is administered to the warm-blooded animal in need of such treatment (p.17, para.1). Zimmerman et al. discloses that effective doses will depend upon the species, age, individual condition, and mode of administration employed, but teaches exemplary doses of about 1-2500 mg, preferably 1-1000 mg, especially 5-500 mg, per 70 kg bodyweight (i.e., for a 70 kg average human, this would correspond to a dose of 5-500 mg, which meets Applicant's claimed dosage amount(s) as recited in instant claim 4; p.17, para.1). An exemplary study of an oral dose of 50 mg/kg once daily of the disclosed compound was shown to inhibit the angiogenic effect of VEGF (p.16, para.2).

Zimmerman et al. fails to teach the treatment of anaplastic thyroid carcinoma (claim 3) or the administration once daily for a period exceeding three months (claim 6).

Ramsden teaches that thyroid cancer cells secrete more VEGF than normal thyrocytes and that expression of VEGF *in vitro* has been shown to correlate to the *in vivo* aggressiveness of the tumor, with anaplastic tumors of the thyroid having the greatest level of expression of VEGF (col.2, para.2, p.476). Ramsden further teaches that VEGF is a significant component of the regulation of angiogenesis within the thyroid (col.1, para.2, p.477).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use the methanesulfonate salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyrid-3-yl)pyrimidin-2-ylamino)phenyl]benzamide for the treatment of anaplastic thyroid carcinoma with a reasonable expectation of success because Zimmerman et al. expressly teaches it as an antitumor agent with the ability to inhibit VEGF and Ramsden teaches the significant expression of VEGF in anaplastic thyroid carcinoma for neovascularization and angiogenesis to encourage metastatic growth of the tumor. Motivation to do so flows logically from the fact that a reduction in VEGF expression would, in turn, reduce the neovascularization and angiogenic process so as to retard proliferation and metastatic tumor growth.

Regarding the instantly claimed dosing schedule (i.e., once daily for a period exceeding three months; claim 6), Zimmerman et al. expressly teaches that the effective doses will vary, depending upon a variety of factors, such as the species, age, individual condition, and mode of administration. Please see p.17, para.1 of Zimmerman et al.

It is obvious from the above teachings that Zimmerman et al. expressly contemplates variation in the dosage amounts and schedule of the active agents. The determination of the optimal dosage amounts and/or schedule of administration would have been a matter well within the skill of the artisan at the time of the invention and would not have required undue experimentation or have been outside the realm of

knowledge generally available to the skilled artisan. Factors that would have been taken into consideration when making such a determination would have included, but not been limited to, the age, weight, sex, diet and medical condition of the patient, severity of the disease, route of administration, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the schedule of administration that would have actually been employed would have been expected to vary widely and, in the absence of evidence to the contrary, would not have been inconsistent with that which is presently claimed. Furthermore, one of skill in the art would have also appreciated that extended treatment with such an antitumor agent would have increased the likelihood of tumor regression and the possibility of remission due to the chronic nature of the condition.

Conclusion

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Please reference U.S. Patent Application Publication No. 2003/0185831 to Cutler et al. ("Methods of Treating Cancer Using an FPT Inhibitor and Antineoplastic").

Rejection of claims 1-8 is proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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February 19, 2009

/Ardin Marschel/
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